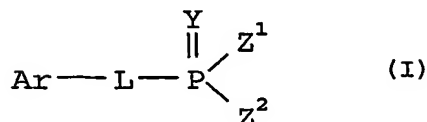
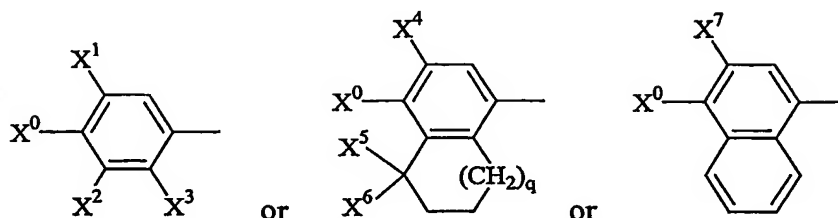


CLAIMS

1. A substituted phosphonate compound of the formula (I):



wherein Ar is:



and X^0 is H, OH or a straight or branched C_1 to C_6 alkoxy group,

X^1 , X^2 and X^3 are independently H, OH, a straight, branched, or cyclic C_1 - C_6 alkyl or alkoxy group;

or X^0 , X^1 or X^2 , X^3 together may form a C_1 - C_8 optionally substituted alkylidenoxy or alkylidenedioxy group;

with the proviso that X^0 is H when X^3 is H and X^1 and X^2 are independently straight or branched C_1 - C_6 alkyl groups;

X^4 , X^5 , X^6 are independently H, a straight or branched C_1 - C_6 alkyl group; q is zero or 1;

X^7 is H, a straight or branched C_1 - C_8 alkyl or alkoxy group, or an optionally substituted benzyl group;

Y is O or S;

Z^1 and Z^2 are independently OR^1 or NR^2R^3 , where R^1 , R^2 , and R^3 are independently H or a straight or branched C_1 - C_6 alkyl group, or Z^1 , Z^2 together may form a C_2 - C_8 alkylidenedioxy group; and

L is a saturated or unsaturated C_1 - C_{11} alkylene chain in which one or more of the methylene groups can be replaced by a sulfur atom, an oxygen atom, a carbonyl group wherein optionally one or more methylene groups can be substituted by one or more halogen atoms F, Cl or Br, C_{1-6} alkyl, an optionally substituted aryl or heteroaryl group;

and pharmaceutically acceptable salts, solvates and hydrates thereof.

2. The compound of claim 1, wherein L is -A-C(O)-B- and A is a direct bond, -CH=C(R⁴)-, -CH₂-C(R⁴)(R⁵)-, -C(R⁴)(R⁵)-, -O-C(R⁴)(R⁵)-, -S-C(R⁴)(R⁵)-, where R⁴, R⁵ are independently H, F, Cl, Br, C₁ - C₆ straight or branched alkyl, or an optionally substituted aryl or heteroaryl, and B is -C(R⁶)(R⁷)- where R⁶, R⁷ are independently H, F, Cl, Br, C₁ - C₆ straight or branched alkyl, or an optionally substituted aryl or heteroaryl, or R⁶ and R⁷ can form a saturated ring of C₃ - C₇ carbon atoms.
3. The compound of claim 2, wherein A is a direct bond, -CH=C(R⁴)-, -CH₂-C(R⁴)(R⁵)- and R⁴ and R⁵ are H, and R⁶ and R⁷ are independently H, F, CH₃, C₂H₅ or R⁶ and R⁷ together form cyclic C₅H₈.
4. The compound of claim 2, wherein A is a direct bond, -CH=CH-, or -CH₂-CH₂-.
5. The compound of claim 4, wherein B is -CH₂-, -CF₂-, -CH(CH₃)-, -CF(CH₃)-, -C(CH₃)₂-, -C(CH₃)(C₂H₅)-, -C(C₂H₅)₂- or -CH(c C₅H₈)-.
6. The compound of claim 1, wherein Y is O.
7. The compound of claim 6, wherein X⁴ is butyl and X⁵ is H or methyl and q is 1.
8. The compound of claim 7, wherein X⁴ is tert-butyl and X⁵ is H.
9. The compound of claim 8, wherein Z¹ and Z² are the same and are OR¹.
10. The compound of claim 9, wherein R¹ is methyl, ethyl or isopropyl.
11. The compound of claim 1, wherein said substituted phosphonate compound of the formula (I) is selected from the group consisting of:
 - dimethyl 4-(3-methoxy-5-methyl-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
 - dimethyl 4-(3,5-dimethoxy-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
 - dimethyl 4-(3,4,5-trimethoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
 - dimethyl 4-(4,5-dimethoxy-3-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

- dimethyl 4-(3,5-diethoxy-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
dimethyl 4-(4-hydroxy-3-methoxy-5-n-propylphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
dimethyl 4-(5-tert-butyl-2-hydroxy-3-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
5 dimethyl 4-(3-cyclopentyloxy-4-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
dimethyl 4-(3,5-di-cyclopentyl-4-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
diethyl 2-(3,4,5-trimethoxyphenyl)-1,1-dimethyl-2-oxo-ethylphosphonate;
10 dimethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-diethyl-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-diethyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-cyclopentyliden-2-oxo-3-buten-1-yl
15 phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-cyclopentyliden-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl phosphonate;
20 dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;
diisopropyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl
25 phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1-methyl-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1-methyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl
phosphonate;
30 diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-difluoro-2-oxo-3-buten-1-yl phosphonate;
diethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-difluoro-2-oxo-3-buten-1-yl phosphonate;
dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-diethyl-2-oxo-3-buten-1-yl phosphonate;

- dimethyl 4-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-cyclopentyliden-2-oxo-3-buten-1-yl phosphonate;
- diethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1-methyl-2-oxoethylphosphonate;
- diethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1,1-dimethyl-2-oxoethylphosphonate;
- 5 dimethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1-fluoro-1-methyl-2-oxoethylphosphonate;
- diethyl 2-(3,5-di-tert-butyl-2-methoxyphenyl)-1-fluoro-1-methyl-2-oxoethylphosphonate;
- dimethyl 4-(3,5-di-tert-butylphenyl)-2-oxo-3-buten-1-yl phosphonate;
- diethyl 4-(3,5-di-tert-butylphenyl)-2-oxo-3-buten-1-yl phosphonate;
- dimethyl 4-(3,5-di-tert-butylphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;
- 10 diethyl 4-(3,5-di-tert-butylphenyl)-1,1-dimethyl-2-oxo-3-buten-1-yl phosphonate;
- dimethyl 4-(3,5-di-tert-butylphenyl)-1-ethyl-1-methyl-2-oxo-3-buten-1-yl phosphonate;
- dimethyl 4-(3,5-di-tert-butylphenyl)-1,1-diethyl-2-oxo-3-buten-1-yl phosphonate;
- dimethyl 4-(3,5-di-tert-butylphenyl)-1,1-cyclopentyliden-2-oxo-3-buten-1-yl phosphonate;
- dimethyl 4-(3,5-di-tert-butylphenyl)-1,1-fluoro-2-oxo-3-buten-1-yl phosphonate;
- 15 diethyl 4-(3,5-di-tert-butylphenyl)-1,1-fluoro-2-oxo-3-buten-1-yl phosphonate;
- dimethyl 2-(3,5-di-tert-butylphenyl)-1-methyl-2-oxoethylphosphonate;
- diethyl 2-(3,5-di-tert-butylphenyl)-1-methyl-2-oxoethylphosphonate;
- dimethyl 2-(3,5-di-tert-butylphenyl)-1,1-dimethyl-2-oxoethylphosphonate;
- diethyl 2-(3,5-di-tert-butylphenyl)-1,1-dimethyl-2-oxoethylphosphonate;
- 20 dimethyl 2-(3,5-di-tert-butylphenyl)-1-fluoro-1-methyl-2-oxoethylphosphonate;
- diethyl 2-(3,5-di-tert-butylphenyl)-1-fluoro-1-methyl-2-oxoethylphosphonate;
- dimethyl 2-(3,5-di-tert-butylphenyl)-1,1-difluoro-2-oxoethylphosphonate;
- dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl phosphonate;
- 25 diethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl-phosphonate;
- dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
- diethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
- 30 dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate;
- diethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate;

- dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl-phosphonate;
- diethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl-phosphonate;
- 5 dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1-ethyl-1-methyl-2-oxo-3-buten-1-yl-phosphonate;
- dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-diethyl-2-oxo-3-buten-1-yl-phosphonate;
- dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-cyclopentylidene-2-oxo-3-buten-1-yl-phosphonate;
- 10 dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl-phosphonate;
- diethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-2-oxo-3-buten-1-yl-phosphonate;
- dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
- 15 diethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
- diisopropyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;
- 20 dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate;
- diethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxo-3-buten-1-yl-phosphonate;
- dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl-phosphonate;
- 25 diethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-fluoro-1-methyl-2-oxo-3-buten-1-yl-phosphonate;
- dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-ethyl-1-methyl-2-oxo-3-buten-1-yl-phosphonate;
- 30 dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-diethyl-2-oxo-3-buten-1-yl-phosphonate;
- dimethyl 4-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1,1-cyclopentylidene-2-oxo-3-buten-1-yl-phosphonate;
- diethyl 2-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-methyl-2-oxoethyl phosphonate;

diethyl 2-(3-tert-butyl-4-methoxy-5,6,7,8-tetrahydronaphthyl)-1-fluoro-1-methyl-2-oxo-ethylphosphonate;

dimethyl 4-(3-tert-butyl-5,5-dimethyl-4-hydroxy-5,6,7,8-tetrahydro-1-naphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

5 dimethyl 4-(3-tert-butyl-4-hydroxy-1-naphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3-benzyl-4-hydroxy-1-naphthyl)-1,1-dimethyl-2-oxo-3-buten-1-yl-phosphonate;

dimethyl 4-(3,5-di-tert-butyl-2-hydroxyphenyl)-1,1-dimethyl-2-oxo-1-butyl-phosphonate;

dimethyl 4-(5-tert-butyl-2-hydroxy-3-methoxyphenyl)-1,1-dimethyl-2-oxo-1-butyl-phosphonate

and dimethyl 4-(3-tert-butyl-4-hydroxy-5,6,7,8-tetrahydronaphthyl)-1,1-dimethyl-2-oxo-

10 1-butyl-phosphonate.

12. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

15 13. A method of treating or preventing a bone disease or pathology by stimulating bone formation, comprising administering to a subject in need of such treatment an amount effective to stimulate bone formation of a substituted phosphonate compound of claim 1.

20 14. The method of claim 13, wherein said bone disease or pathology is selected from the group consisting of osteoporosis, Paget's disease, bone fracture, hormone-induced bone pathologies, hyperparathyroidism, periodontal disease, post-plastic surgery, post-prosthetic joint surgery and post-dental implantation.

25 15. The method of claim 13, wherein said bone disease or pathology comprises hypercalcemia secondary to malignancies or hyperparathyroidism.

16. The method of claim 13, wherein said bone disease or pathology comprises a condition arising from hypercalcemia.

30 17. The method of claim 16, wherein said condition arising from hypercalcemia is selected from the group consisting of calcification of soft tissue, calcification of surgical implants and calcification of arteries.

18. The method of claim 17, wherein said soft tissue is selected from the group consisting of kidney, vessel walls and heart valves.

19. The method of claim 18, wherein said calcification of arteries is due to late stage atherosclerosis.

20. The method of claim 13, wherein said subject is characterized by a condition selected from the group consisting of osteoporosis, Paget's disease, bone fracture or deficiency, drug and hormone-induced bone pathologies, hyperparathyroidism, periodontal disease or defect, post-plastic surgery, post-prosthetic joint surgery and post-dental implantation.

21. The method of claim 20, wherein said drug- and hormone-induced pathology is selected from the group consisting of corticoids, retinoids and vitamin D3-induced bone pathologies.

22. The method of claim 13, wherein said subject is characterized by a condition selected from metastasis of cancer cells in bones, tumoral osteolysis, and hypercalcemia, wherein said hypercalcemia is secondary to malignancies.

23. The method of claim 13, wherein said metastasis of cancer cells in bone is osteolytic or osteoplastic bone metastasis.

24. The method of claim 13, wherein said subject is characterized by a condition selected from periodontal disease or defect, post-plastic surgery, post-prosthetic joint surgery and post-dental implantation.

25. The method of claim 13, further comprising administration to said subject an effective amount of a bone resorption inhibitor.

26. The method of claim 25, wherein said bone resorption inhibitor is selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zoledronate, midronic acid, icandronic acid, S-12911, raloxifene, simvastatin, atorvastatin, cerivastatin, vitamin D and calcitonin.

27. The method of claim 26, wherein said subject is characterized by a condition selected from the group consisting of osteoporosis, Paget's disease, bone fracture or deficiency, drug and hormone-induced bone pathologies, hyperparathyroidism, periodontal disease or defect, post-plastic surgery, post-prosthetic joint surgery and post-dental implantation.

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28. The method of claim 27, wherein said drug- and hormone-induced pathology is selected from the group consisting of corticoids, retinoids and vitamin D3-induced bone pathologies.

29. The method of claim 28, wherein said subject is characterized by a condition selected from metastasis of cancer cells in bones, tumoral osteolysis and hypercalcemia, wherein said hypercalcemia is secondary to malignancies.

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30. The method of claim 29, wherein said metastasis of cancer cells in bone is osteolytic or osteoplastic bone metastasis.

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